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ORIGINAL COMMUNICATION

# Neurological manifestations of Behçet's disease in Japan: a study of 54 patients

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**Abstract** The type and frequency of neurological manifestations of Behçet's disease (BD) vary with ethnicity. We analyzed the neurological manifestations of BD in Japanese patients. All patients undergoing treatment at one of the two Yokohama City University hospitals from July 1991 to December 2007 and who fulfilled the Japanese criteria for BD revised in 1987 were studied retrospectively by chart review. Patients had been neurologically assessed by neurologists. We recorded neurological signs and symptoms, magnetic resonance imaging or computed tomography findings, and results of cerebrospinal fluid examinations from the records of each patient. We studied 412 patients with BD, of whom 54 (13%) had neurological involvement (neuro-Behçet's disease: NB). NB patients included a significantly higher proportion of males (61%) than non-NB patients (42%, $P = 0.009$). The majority of patients ($n = 38$, 70%) had acute parenchymal NB, 15 (28%) had chronic progressive parenchymal NB, and 1 (2%) had the non-parenchymal type. Headache and fever were more frequently reported by patients with acute parenchymal NB. Personality changes, sphincter disturbances, involuntary movements, and ataxia occurred predominantly in patients with chronic progressive parenchymal NB. Lesions were distributed throughout the CNS, but mainly in the brainstem, white matter, and basal ganglia. Analysis of end-point clinical outcomes revealed a poor prognosis for patients with chronic progressive NB. In Japan, most NB patients have the parenchymal type, and male gender is a predisposing factor. Because of the unfavorable prognosis associated with chronic progressive NB, development of effective therapies are urgently needed.

**Keywords** Behçet's disease · Neurological involvement · Acute type · Chronic progressive type · MRI · Japan

**Abbreviations**

| | |
|---|---|
| BD | Behçet's disease |
| CNS | Central nervous system |
| CSF | Cell counts in cerebrospinal fluid |
| CT | Computed tomography |
| EDSS | Expanded Disability Status Scale |
| FLAIR | Fluid attenuated inversion recovery |
| ISG | International Study Group |
| MRI | Magnetic resonance imaging |
| MRV | Magnetic resonance venography |
| NB | Neuro-Behçet's disease |

## Introduction

Behçet's disease (BD) is a multisystem disease characterized by recurrent oral and genital ulcers, relapsing uveitis, and other mucocutaneous, articular, urogenital, intestinal, neurologic, and vascular manifestations. The epidemiology

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of BD varies with geography and is most common along the antique "Silk Road" that extends from the Mediterranean region to Japan [38]. Interestingly, the symptoms of BD also vary geographically, with severe eye involvement and inflammatory bowel disease being more common in the Far East than in the Mediterranean basin, and the pathergy reaction being less frequent in western countries than the Mediterranean region and Japan [42].

Central nervous system (CNS) involvement in BD, usually called neuro-Behçet's disease (NB), is one of the most serious complications of the disease. The frequency of neurological involvement among BD patients varies greatly; in hospital-based series, percentages as low as 1.3% [47] and as high as 59% [11] have been reported, but is likely to be biased for various reasons. The pooled average was 9.4% [3]. An autopsy series of 170 cases of BD showed pathological evidence of neurological involvement in 20% [29]; a similar proportion has been found to have silent neurological involvement, as indicated by magnetic resonance imaging (MRI) [4].

NB either is caused by primary neural parenchymal lesions or is secondary to major vascular involvement [22, 40]. The latter type is rarely associated with primary parenchymal type and should be called vasculo-Behçet's disease [40]. The only geographical variation reported for neurological involvement is for intracranial hypertension, which is more commonly observed in patients of Middle Eastern origin and less common in patients from Japan [4, 20].

In the present retrospective study, we aimed to determine the prevalence of neurological involvement and the patterns of clinical neurological syndromes in patients attending one of two university hospitals in Yokohama, Japan.

## Patients and methods

The study sample included all patients who were treated for BD at the two Yokohama City University Hospitals in the central area of Japan from July 1991 to December 2007. Yokohama City University Hospital is a tertiary referral hospital with 623 beds, and Yokohama City University Medical Center has 720 beds.

We used the Japanese criteria revised in 1987 [35] for diagnosing BD. Recurrent aphthous ulcers of oral mucosa, skin lesions (such as erythema nodosum, acne, and cutaneous hypersensitivity), ocular inflammation, and genital ulcers are major symptoms. Arthritis, intestinal ulcers, epididymitis, vascular lesions (such as obliteration, occlusion, aneurysm), and neuropsychiatric disease are minor symptoms. Those with four major symptoms simultaneously or at different times are defined as complete-type BD patients. Patients with three major symptoms simultaneously or at different times, with two major and two minor symptoms, with typical recurrent ocular inflammation and one or more major symptoms, or with typical recurrent ocular inflammation and two minor symptoms are defined as incomplete-type BD patients. Those patients with one or two major symptoms, who do not satisfy the requirements for the incomplete type, are defined as suspect-type BD patients. We included complete- and incomplete-type patients in our investigations, but excluded suspect-type patients on the grounds that we intended to investigate only patients we were certain had BD.

The 412 records that met the inclusion criteria were analyzed for sex, age at the onset of each BD symptom, age at diagnosis of BD, HLA-B51 positivity, follow-up period, and main attending physician. All patients had undergone detailed medical interviews and routine physical examination by qualified specialists in each field, such as neurologists, ophthalmologists, rheumatologists, dermatologists, or gastroenterologists. Every possible effort was made to rule out conditions that may have simulated BD such as chronic oral aphthosis, herpes simplex virus infection, Sweet's syndrome, and HLA-B27-related syndromes. The medical files were reviewed for clinical findings on regular follow-up. Data on demographic parameters and laboratory results were recorded as well. Clinical features of the patients in the present study were compared with the data from two previous, large, nationwide epidemiological surveys of BD conducted in Japan in 1972 and 1991 [38].

From the 412 records, we identified 54 patients with neurological involvement. Individual neurological manifestations were categorized according to the criteria in previous papers [2, 4]. For each patient, the neurologist determined the appropriate diagnostic protocol according to the clinical findings. Instrumental evaluations included MRI and computed tomography (CT), and the protein levels and cell counts in cerebrospinal fluid (CSF) were also examined.

We classified NB into two major types, parenchymal and non-parenchymal. The parenchymal type was further divided into two subtypes, acute and chronic progressive. The acute type is characterized by acute meningoencephalitis with or without focal lesions which present as high-intensity areas in T2-weighted images or fluid attenuated inversion recovery (FLAIR) images on MRI, responds well to corticosteroids and is usually self-limiting [16, 17, 18]. The chronic progressive type is characterized by intractable, slowly progressive dementia, ataxia, and dysarthria, along with persistent marked elevation of IL-6 in the CSF (usually more than 20 pg/ml) [16, 17, 18]. In the non-parenchymal type, the parenchymal damage is secondary to

a pathological process localized in the large venous or, more rarely, arterial vessels [40, 42].

We evaluated the neurological conditions at the end of follow-up by using Kurtzke's Expanded Disability Status Scale (EDSS) [28]. This is an ordinal scale from 0 to 10, with six representing a moderate disability (patient requires help in walking and during other activities of daily life) and ten representing death. It was originally devised for disability associated with multiple sclerosis. Although the scale has not been validated as a measure of long-term neurological disability in BD, the functional systems involved in the two disorders are similar, and we have used this scale [43]. We divided the NB patients into four groups according to EDSS score: asymptomatic (EDSS = 0), mild ($0 < \text{EDSS} < 3$), moderate ($3 \leq \text{EDSS} < 6$), and severe ($6 \leq \text{EDSS} \leq 10$).

Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). The categorical variables were analyzed by the chi-squared test or Fisher's exact probability test, as appropriate. The continuous variables were analyzed by Student's $t$ test or Welch's $t$ test, as appropriate. A value of $P < 0.05$ was regarded as indicating statistical significance.

Informed consent was obtained from each patient, and the Ethics Committee of the Yokohama City University approved the study protocol.

## Results

Of the 412 patients who met the study criteria, all were Japanese natives except three (one Chinese, one Korean, and one Syrian). One hundred and forty-three patients (35%) were classified to complete-type BD, whereas 269 patients (65%) were classified to incomplete-type BD. The frequencies of clinical manifestations in the patients with BD are given in Table 1. We found significantly lower frequencies of arthritis and gastrointestinal involvement than in the two previous, large surveys [38]. Neurological involvement was observed in 54 BD patients (13%)—almost the same as in the previous studies. Of them, 23 patients were classified as complete-type BD (16% of all complete-type patients), while the remaining 31 patients were classified as incomplete-type BD (12% of all incomplete-type patients). Four patients were not defined as incomplete-type BD if they had not complicated with neurological involvement. Because all NB patients were Japanese, these data can be considered representative of Japanese NB patients.

Compared with patients without NB, NB patients were more likely to be male (61% in NB vs. 42% in non-NB, $P = 0.009$) and to have eye involvement (78% in NB vs. 63% in non-NB, $P = 0.029$; Table 2). NB patients had a lower percentage of genital ulcers (61% in NB versus 74% in non-NB, $P = 0.043$).

**Table 1** Comparison of frequency of individual clinical manifestations in the present study with the previous two large nationwide epidemiological surveys for BD in Japan

| Clinical features | Japan (1972) $n = 2{,}031$ | Japan (1991) $n = 3{,}316$ | Present study $n = 412$ |
|---|---|---|---|
| Major symptoms | | | |
| Oral ulcer | 96[†] | 98[¶] | 99.5 |
| Genital ulcer | 72 | 73 | 72.6 |
| Eye involvement | 67 | 69 | 64.6 |
| Skin involvement | 83[¶] | 87 | 88.1 |
| Minor symptoms | | | |
| Arthritis | 54[¶] | 57[‡] | 48.1 |
| Epididymitis | 6 | 6 | 6.0 |
| Gastrointestinal involvement | 25[†] | 16[‡] | 10.4 |
| Central nervous involvement | 13 | 11 | 13.1 |
| Vascular involvement | 7 | 9 | 7.8 |

[†] $P < 0.001$, [‡] $P < 0.01$, [¶] $P < 0.05$

Of the 54 NB patients, parenchymal NB occurred in 53 patients, 38 (70%) with acute type and 15 (28%) with chronic progressive type (Table 3). Male predominance was found in both subtypes, but with an even higher predominance of males in the chronic progressive type (55% in the acute type, and 73% in the chronic progressive type). Non-parenchymal NB occurred in one patient. There was a family history of BD in one patient in whom the acute type of NB occurred twice.

Patients with NB had a variety of neurological signs and symptoms (Table 4). Headache ($P = 0.003$) and fever ($P = 0.046$) were significantly more prevalent in patients with the acute type. In contrast, personality changes ($P < 0.001$), sphincter disturbances ($P = 0.001$), involuntary movements ($P = 0.005$), and ataxia ($P = 0.013$) were significantly more prevalent in patients with the chronic progressive type.

We noted the distribution of neurological lesions that had been determined by clinical examinations, including MRI or CT. Imaging results were available for all NB patients except three patients with the acute type. Lesions were distributed throughout most of the central nervous system, but occurred more frequently in brainstem, white matter, and basal ganglia (Table 5). The images from all patients with the chronic progressive type showed some abnormal findings, whereas no abnormality was detected in 10 of 35 (29%) of acute-type patients ($P = 0.021$). Although the brainstem and cerebral white matter were most commonly affected in both the acute and chronic

**Table 2** Comparison of clinical features between NB patients and the others

| | With CNS involvement ($n = 54$) | Without CNS involvement ($n = 358$) | All | $P$ |
|---|---|---|---|---|
| Age at disease onset (years, mean ± SD) | 35.8 ± 10.3 | 37.0 ± 12.1 | 36.9 ± 11.9 | NS |
| Male sex | 33 (61%) | 151 (42%) | 184 (45%) | 0.009 |
| Interval between the symptom onset and diagnosis of BD (years, mean ± SD) | 8.1 ± 9.4 | 8.7 ± 10.2 | 8.6 ± 10.1 | NS |
| Follow up duration (years, mean ± SD) | 7.5 ± 6.7 | 7.1 ± 6.7 | 7.2 ± 6.7 | NS |
| Median (range) | 5.9 (0.0–25.3) | 5.1 (0.0–37.1) | 5.2 (0.0–37.1) | |
| HLA-B51 positivity | 16/29 (55%) | 107/217 (49%) | 123/246 (50%) | NS |
| Oral ulcer | 54 (100%) | 356 (99%) | 410 (100%) | NS |
| Genital ulcer | 33 (61%) | 266 (74%) | 299 (73%) | 0.043 |
| Eye involvement | 42 (78%) | 224 (63%) | 266 (65%) | 0.029 |
| Skin involvement | 45 (83%) | 318 (89%) | 363 (88%) | NS |
| Arthritis | 20 (37%) | 178 (50%) | 198 (48%) | NS |
| Epididymitis | 4/33 (12%) | 7/151 (5%) | 11/184 (6%) | NS |
| Gastrointestinal involvement | 2 (4%) | 41 (12%) | 43 (10%) | NS |
| Vascular involvement | 2 (4%) | 30 (8%) | 32 (8%) | NS |

**Table 3** Baseline characteristics of 54 neuro-Behçet's (NB) patients

| Characteristics | 54 NB, mean (SD) or $n$ (%) | Acute NB ($n = 38$) | Chronic progressive NB ($n = 15$) | 358 non-NB, mean (SD) or $n$ (%) |
|---|---|---|---|---|
| Male sex | 33 (61%)[a] | 21 (55%) | 11 (73%)[b] | 151 (42%) |
| Age at BD diagnosis (years) | 35.8 ± 10.3 | 34.8 ± 10.7 | 38.2 ± 10.9 | 37.0 ± 12.1 |
| Age at the first neurological episode (years) | 39.8 ± 11.2 | 38.1 ± 9.9 | 44.4 ± 13.6 | – |
| BD duration before neurological involvement (years) | 4.1 ± 7.3 | 3.3 ± 5.5 | 6.2 ± 10.7 | |
| Neurological symptoms as the initial BD manifestation | 3 (6%) | 1 (3%) | 2 (13%) | – |
| Follow-up duration (years) | 7.5 ± 6.7 | 8.8 ± 6.3 | 4.6 ± 7.1 | 7.1 ± 6.7 |
| Median (range) | 5.9 (0.0–25.3) | 8.3 (0.0–25.3) | 1.7 (0.1–24.5) | 5.1 (0.0–37.1) |
| HLA-B51 positivity | 17/29 (57%) | 12/21 (57%) | 5/7 (71%) | 107/217 (49%) |

[a] Compared with non-NB patients, NB patients showed higher percentage of male sex ($P = 0.009$)

[b] Compared with non-NB patients, chronic progressive NB patients showed higher percentage of male sex ($P = 0.017$)

progressive types, the features of the lesions were different between the two groups. T2 high-intensity signals were found mainly in the brainstem and white matter in patients with acute type, whereas brainstem atrophy was prominent, and cerebral atrophy and enlarged ventricles were common in patients with the chronic progressive type, as previously shown [23]. Most of these findings were comparable with those from similar studies from other countries, except for a higher incidence of white matter lesions and a lower incidence of thalami lesions in our study (Table 5) [2, 25, 31, 32].

Cerebrospinal fluid (CSF) from 21 patients with acute NB and 11 patients with chronic progressive NB was examined. Patients with the acute type had significantly more CSF cells than patients with the chronic progressive type (272/mm$^3$ vs. 29/mm$^3$, $P = 0.032$), but there were no significant differences in CSF protein concentration (62 mg/dl in acute type vs. 62 mg/dl in chronic progressive type, $P > 0.05$) or opening pressure (17.5 vs. 13.9 cm$H_2O$, $P > 0.05$). The single patients with non-parenchymal NB, a 36-year-old male, had elevated CSF opening pressure (50 cm$H_2O$) with normal CSF constituents (CSF cells: 6/mm$^3$; CSF protein: 31 mg/dl), reflecting the underlying transverse sinus thromboses, identified by magnetic resonance venography (MRV).

Although all of the patients had neurological involvement, drug therapy was often primarily directed at concurrent systemic features; multiple therapies were

**Table 4** Comparison of cumulative neurological signs and symptoms between acute NB patients and chronic progressive NB patients

| Neurological findings | Acute NB ($n = 38$) | Chronic progressive NB ($n = 15$) | $P$ |
|---|---|---|---|
| Headache | 25 (66%) | 3 (20%) | 0.003 |
| Fever | 16 (42%) | 2 (13%) | 0.046 |
| Personality changes | 3 (8%) | 14 (93%) | <0.001 |
| Sphincter disturbances | 4 (11%) | 8 (53%) | 0.001 |
| Involuntary movements | 3 (8%) | 6 (40%) | 0.005 |
| Ataxia | 4 (11%) | 6 (40%) | 0.013 |
| Pyramidal signs and symptoms | 21 (55%) | 10 (67%) | NS |
| Speech disorder | 13 (34%) | 7 (47%) | NS |
| Cranial nerves | 10 (26%) | 6 (40%) | NS |
| Disorders of sensation | 10 (26%) | 4 (27%) | NS |
| Meningeal signs | 8 (21%) | 1 (7%) | NS |
| Cerebellar signs | 7 (18%) | 4 (27%) | NS |
| Dysphagia | 3 (8%) | 4 (27%) | NS |
| Epileptic fits | 3 (8%) | 1 (7%) | NS |

**Table 5** Distribution of neurological lesions determined by clinical examinations including MRI or CT

| Neurological lesions | Acute NB ($n = 35$) | Chronic progressive NB ($n = 15$) | $P$ | Turkey [25] ($n = 65$) | Turkey [2] ($n = 162$) | Korea [31] ($n = 21$) | North Italia [32] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Acute ($n = 21$) | Remission ($n = 13$) |
| Brain stem | 21 (60%) | 11 (73%) | NS | 56 (86%) | 83 (51%) | 18 (86%) | 8 (38%) | 1 (8%) |
| White matter | 18 (51%) | 10 (67%) | NS | 4 (6%) | 25 (15%) | 9 (43%) | 8 (38%) | 9 (69%) |
| Basal ganglia | 6 (17%) | 2 (13%) | NS | 12 (18%) | | 9 (43%) | 8 (38%) | 0 |
| Cerebellum | 5 (14%) | 2 (13%) | NS | 3 (5%) | | | 4 (15%) | 0 |
| Spinal cord | 2 (6%) | 2 (13%) | NS | 3 (5%) | 23 (14%) | 2 (10%) | 5 (24%) | 0 |
| Thalamus | 5 (14%) | 0 | NS | 15 (23%) | | 6 (29%) | | |
| Cranial nerve | 1 (3%) | 0 | NS | 1 (2%) | | | | |
| Normal findings | 10 (29%) | 0 | 0.021 | | 10 (6%) | | 3 (14%) | 4 (31%) |

administered sequentially for some patients because of their inability to tolerate a particular drug or toxicity, so that the efficacy of treatment for neurological symptoms was difficult to assess. Prednisone (35 patients), including methylprednisolone pulse (14 patients), was the most commonly used therapy (Table 6). Immunosuppressants were also prescribed: four patients were prescribed azathioprine, three patients were prescribed methotrexate, and one patient each was prescribed cyclophosphamide and cyclosporine. A total of 22 patients received colchicine for associated mucocutaneous manifestations or arthritis rather than for neurological involvement.

Forty-four patients (81%) had any attack with neurological features. Among those with the acute type, 27 patients (71%) had single attacks and 11 patients (29%) had relapses: seven patients had one relapse, two patients had two relapses, and two patients had five relapses. Of those with the chronic progressive type, nine patients (60%) had no attack, three patients (20%) had single attacks, and three patients (20%) had relapses; two patients each had two relapses, and one patient had three relapses.

We examined the neurological condition at the end of follow-up by using the EDSS [28]. The mean EDSS at the end of follow-up times was $1.6 \pm 2.5$ in patients with the acute type, and $5.3 \pm 2.6$ in patients with the chronic progressive type ($P < 0.001$). Of patients with the acute type, 28 (74%) were classified into the asymptomatic or mild groups. In contrast, 13 patients (87%) with the chronic progressive type were classified into the moderate or severe groups. By the time of the analysis, two patients with chronic progressive NB had died from neurological complications.

We analyzed clinical features which were associated with severe neurological conditions ($6 \leq \text{EDSS} \leq 10$). In these patients, following neurological manifestations were more frequently reported ; personality changes ($P = 0.015$), sphincter disturbances ($P = 0.001$), ataxia ($P = 0.017$), speech disorder ($P = 0.049$), and dysphagia

**Table 6** Comparison of therapy among acute and chronic progressive NB

| | Acute NB ($n = 38$) | Chronic progressive NB ($n = 15$) | *P* |
|---|---|---|---|
| Prednisone (PSL) | 25 (66%) | 10 (67%) | NS |
| Methylprednisolone pulse (mPSL) | 11 (29%) | 3 (20%) | NS |
| Withdrawal previous therapy (WD) | 9 (24%) | 1 (7%) | NS |
| Azathioprine (AZP) | 3 (8%) | 1 (7%) | NS |
| Methotrexate (MTX) | 2 (5%) | 1 (7%) | NS |
| Infliximab (IFX) | 1 (3%) | 0 | NS |
| Cyclophosphamide (CP) | 1 (3%) | 0 | NS |
| Intravenous immunoglobulin (IVIG) | 1 (3%) | 0 | NS |
| Cyclosporine (CSA) | 0 | 1 (7%) | NS |
| Colchicine (COL) | 17 (45%) | 5 (33%) | NS |
| Observation | 6 (16%) | 1 (7%) | NS |

($P = 0.019$). Among abnormal imaging findings of MRI or CT, spinal cord lesions ($P = 0.026$) and brainstem atrophy ($P = 0.003$) were significantly detected in patients having severe neurological conditions. However, there were no associations of cerebrospinal findings, gender, or frequency of attacks with high score of EDSS.

## Discussion

Our study reports on the clinical features of a large sample of predominantly Japanese adult patients with BD seen in two university hospitals over 16.5 years. We described the neurological features of 54 Japanese patients with BD—empirically not a large number. Although our study was limited by being retrospective, and it was hard to avoid severity bias caused by the selection of patients with more severe disease and/or multiple organ involvement; nevertheless as a hospital-based investigation this provided a unique opportunity to review the full spectrum of disease manifestations. Indeed, this was the largest cohort of NB patients with this ethnic background, with the longest period of follow-up among any published series.

The diagnosis of BD remains mostly clinical, and currently the most widely used diagnostic tool is the International Study Group (ISG) classification [1]. In Japan, however, the diagnostic criteria for Behçet's disease established by the Behçet's Disease Research Committee of Japan [35] are widely used. Unlike the ISG classification, the Japanese criteria include organ lesions in the gastrointestinal tract, central nervous system, and large vessels as minor symptoms. These manifestations are less common than oculomucocutaneous symptoms, which are considered major, but they are often serious, so that any delay in diagnosis could have serious effects. The sensitivity, specificity, and accuracy of the Japanese criteria are 80.6, 95.3, and 88.3%, respectively, and those of the ISG criteria are 79.4, 99.4, and 89.8%, respectively [10].

We found central nervous system involvement in 13% of the 412 BD patients. This frequency is almost the same as that reported in previous epidemiological studies in Japan [38], suggesting that our group was representative of Japanese BD patients. The previous studies were based on simple questionnaires and did not include the details of neurological manifestations in individual patients. Our detailed chart review found a predominance of males among NB patients, a low frequency of the non-parenchymal type, and poor prognosis for patients with the chronic progressive type.

The male predominance of NB patients is consistent with the findings of previous large-scale studies, which reported male-to-female ratios of neurological involvement in BD of 1.6 [22] to 3.8 [43]. A male predominance has also been noted for vascular complications of BD [27].

HLA-B51 is well established as a genetic marker of BD. This association has been confirmed in different ethnic groups [8, 24, 34], although its pathogenic role in BD remains unknown [48]. Although several extensive studies have examined the association of HLA-B51 with particular manifestations, including uveitis and disease severity, the data conflict and the connections remain unclear [7, 44]. Consistent with a report by Gul et al. from Turkey [12], our results showed no difference in the frequency of HLA-B51 between NB patients and non-NB patients, irrespective of whether the NB was of the acute or chronic progressive type. However, HLA phenotypes were available in only 7 of 15 patients with the chronic progressive type. In fact, although 5 of the 7 (71%) were HLA-B51 positive, the data were not statistically significant, perhaps because of the small sample size. Aramaki et al. [5] detected HLA-B51 in 16 of 17 Japanese NB patients (94%) with the chronic progressive type.

Our data revealed a higher frequency of eye involvement in NB patients than in non-NB patients, whereas genital ulcers were less frequent. These results are not consistent with the results of Tunisia by Houman et al. [19], who found that genital ulcers were significantly more frequent in NB patients than in non-NB patients, but that the frequency of eye involvement did not differ between NB patients and non-NB patients. High frequency of ocular involvement in NB patients may be caused by therapeutic regimen for ocular lesions in our patients. In Japan, azathioprine, which is listed as the first line agent for ocular disease affecting posterior segment [14], is infrequently

used, whereas cyclosporine A (CSA) is more commonly used than in other countries. While azathioprine has been shown to suppress neurological involvement [13, 15], CSA has a potential neurotoxicity for BD patients [26]. Alternatively, the discrepancy may reflect the ethnic difference between Japan and Tunisia. To clarify this issue, an international comparative study is necessary.

We found some differences between our NB patients and those reported in other countries. Neurological presentation as an initial manifestation of BD was seen in three patients (6%) in our series; all three were men. This is comparable to the 3% seen in a larger Turkish study [2] and 10% in an Arab series [4], but it is lower than the 23–30% in series of Afro-Caribbeans [30], Iranians [6], Londoners of mixed ethnicity [22], and people in the south-west of England [21]. We speculate that these regional differences reflect differences in the diagnostic threshold among the regions, rather than a true phenotypic heterogeneity. Because physicians in endemic areas, such as Turkey and Japan, are more familiar with the disease, even minor systemic presentations are considered to be a part of the disease manifestations before the onset of neurological symptoms [21].

Although only one patient (2%) had the non-parenchymal type of neurological disease in our study, the reported frequency of non-parenchymal NB patients ranges from 10 to 20% [42]. The higher rates have been reported in a limited number of clinical studies [4, 39], but the different geographical regions and ethnic backgrounds of the patients in these studies make comparing these rates difficult. The pathogenesis of thrombosis in BD is unknown, although multiple factors likely contribute to it. The factor V Leiden mutation [9, 45] and G20210A mutation in the 3′-untranslated region of the prothrombin gene [33], which are associated with thrombophilia, are rare in the Japanese population [46] and are not found in Japanese patients with pulmonary thromboembolism [37]. However, the contributions of these genetic factors to thrombogenesis in BD are controversial [36, 41], and other factors may play more critical roles.

In concordance with previous reports, our study showed a poor prognosis in patients with chronic progressive NB. Most the chronic progressive type NB patients (13 of 15, 87%) were classified as having moderate or severe disease, and the two patients died from neurological problems. Unfavorable clinical outcome in chronic progressive type is associated with brainstem atrophy, as previously shown [23]. Moreover, because the present study was of a retrospective design, decisions about therapies were made by the individual attending physicians. Analysis of therapeutic agents revealed that infrequent usage of immunosuppressants may have been partly responsible for the poor outcomes in patients with chronic progressive type of NB in the present study, although no effective therapies for NB have yet been developed [14, 15].

Further assessment of our patients may allow us to detect early predictors of aggressive disease that could highlight a subgroup that requires more intensive treatment. In the meantime, we eagerly await effective therapies for NB—especially the chronic progressive type.

## Conclusion

In Japan, most NB patients have the parenchymal type, and male gender is a predisposing factor. Because of the unfavorable prognosis associated with chronic progressive NB, there is an urgent need to develop effective therapies for this disease.

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